(3) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 0.7 milligram per milliliter.

(4) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

(5) *Specific rotation.* Dissolve and dilute an accurately weighed sample with sufficient 2 percent sodium bicarbonate to obtain a concentration of approximately 10 milligrams of cefixime per milliliter. Proceed as directed in §436.210 of this chapter, using a 1.0-decimeter polarimeter tube. Calculate the specific rotation on the anhydrous basis.

(6) *Identity.* Proceed as directed in §436.211 of this chapter, using a potassium bromide disc containing 0.5 percent of cefixime. Dissolve 5 to 6 milligrams of cefixime in 2 milliliters of methanol. Triturate to insure solution. Evaporate the solvent to dryness and using the dried sample, prepare the potassium bromide disc.

[53 FR 24257, June 28, 1988; 53 FR 26712, July 14, 1988; 54 FR 47205, Nov. 13, 1989]

§442.16 Ceftazidime pentahydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ceftazidime pentahydrate is pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[1-carboxy-1-methylethoxy)imino]acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6*R*-[6α,7β(*Z*)]]-, pentahydrate. It is so purified and dried that:

(i) Its potency is not less than 950 micrograms and not more than 1,020 micrograms of ceftazidime activity per milligram on an anhydrous basis.

(ii) Its loss on drying is not less than 13.0 percent and not more than 15.0 percent.

(iii) The pH of an aqueous solution containing 5 milligrams of ceftazidime per milliliter is not less than 3.0 and not more than 4.0.

(iv) It is crystalline.

(v) It gives a positive identity test for ceftazidime.

(vi) Its high molecular weight polymer content is not more than 0.05 percent.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, loss on drying, pH, crystallinity, identity, and high molecular weight polymer content.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §442.16a(b)(1).

(2) *Loss on drying.* Proceed as directed in §436.200(a) of this chapter.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 5 milligrams of ceftazidime per milliliter.

(4) *Crystallinity.* Proceed as directed in §436.203(a) of this chapter.

(5) *Identity.* The high performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the ceftazidime working standard.

(6) *High molecular weight polymer content.* Proceed as directed in §442.16a(b)(8).

[54 FR 40652, Oct. 3, 1989]

§442.16a Sterile ceftazidime pentahydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile ceftazidime pentahydrate is pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6*R*-[6α, 7β(*Z*)]]-, pentahydrate. It is so purified and dried that:

(i) Its potency is not less than 950 micrograms and not more than 1,020 micrograms of ceftazidime activity per milligram on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its loss on drying is not less than 13.0 and not more than 15.0 percent.

(v) Its pH in an aqueous solution containing 5 milligrams of ceftazidime per milliliter is not less than 3.0 and not more than 4.0.

(vi) It is crystalline.

(vii) It gives a positive identity test for ceftazidime.

(viii) Its high molecular weight polymer content is not more than 0.05 percent.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain.

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, crystallinity, identity, and high molecular weight polymer content.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(*a*) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(*b*) For sterility testing: One package containing approximately 6 grams of a composite sample.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in §436.356 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as hexyl, octyl, or octaldecyl hydrocarbon bonded silicas, a flow rate of 2.0 milliliters per minute, and a known injection volume of 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(*a*) *Phosphate buffer, pH 7.0.* Dissolve 42.59 grams of sodium phosphate, dibasic anhydrous and 27.22 grams of potassium phosphate, monobasic, in water and dilute to 1,000 milliliters.

(*b*) *Mobile phase.* Mix 40 milliliters of acetonitrile and 200 milliliters of phosphate buffer, pH 7.0, and dilute to 2,000 milliliters with water. Filter the mobile phase through a suitable glass fiber filter or equivalent that is capable of removing particulate contamination to 1 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph pumping system.

(ii) *Preparation of working standard and sample solutions*—(*a*) *Working standard solution.* Accurately weigh ceftazidime working standard equivalent to approximately 100 milligrams of the ceftazidime activity into a 100-milliliter volumetric flask containing 10 milliliters of phosphate buffer, pH 7.0. Shake until dissolved. Dilute to volume with water to obtain a stock solution containing approximately 1,000 micrograms of ceftazidime activity per milliliter. Mix well. Immediately prior to chromatography, further dilute 5 milliliters of stock solution to 50 milliliters with water to obtain a solution containing 100 micrograms of ceftazidime activity per milliliter.

(*b*) *Sample solution.* Accurately weigh approximately 115 milligrams of the sample into a 100-milliliter volumetric flask containing 10 milliliters of phosphate buffer, pH 7.0. Shake until dissolved. Dilute to volume with water to obtain a stock solution containing approximately 1,000 micrograms of ceftazidime per milliliter. Mix well. Immediately prior to chromatography, further dilute 5 milliliters of stock solution to 50 milliliters with water to obtain a solution containing 100 micrograms of ceftazidime activity per milliliter (estimated).

(iii) *System suitability requirements*—(*a*) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.5 at 5 percent of peak height.

(*b*) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 1,500 theoretical plates.

(*c*) *Resolution.* The resolution (*R*) between the peak for ceftazidime and its nearest eluting impurity is satisfactory if it is not less than 2.0.

(*d*) *Coefficient of variation.* The coefficient of variation (S_R in percent) of five replicate injections is satisfactory if it is not more than 1.0 percent.

If the system suitability requirements have been met, then proceed as described in §436.356(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility

and resolution are provided comparable to the system. However, the sample preparation described in paragraph (b)(1)(ii)(*b*) of this section should not be changed.

(iv) *Calculations.* Calculate the micrograms of ceftazidime per milligram of sample as follows:

$$\text{Micrograms of ceftazidime per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u (100 - m)}$$

where:

A_u=Area of the ceftazidime peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the ceftazidime peak in the chromatogram of the ceftazidime working standard;

P_s=Ceftazidime activity in the ceftazidime working standard solution in micrograms per milliliter;

C_u=Milligrams of sample per milliliter of sample solution; and

m=Percent loss on drying content of the sample.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except dissolve the sample in approximately 200 milliliters of diluting fluid H.

(3) *Pyrogens.* Proceed as directed in § 436.32(i) of this chapter, using a solution containing 80 milligrams of ceftazidime per milliliter.

(4) *Loss on drying.* Proceed as directed in § 436.200(a) of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 5 milligrams of ceftazidime per milliliter.

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(7) *Identity.* The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the ceftazidime working standard.

(8) *High molecular weight polymer content.* Proceed as directed in § 436.360 of this chapter, using a constant temperature between 20 and 25 °C, an ultraviolet detection system operating at a wavelength of 235 nanometers, a column packed with a hydrophilic gel for gel permeation chromatography (such as Fractogel TSK HW–40(F), Merck) or equivalent, a flow rate of 1.0 milliliter per minute, and a known injection volume of 100 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(*a*) *Mobile phase.* Adjust a 0.1*M* solution of potassium phosphate, dibasic, to pH 7.0±0.1 with phosphoric acid.

(*b*) *Blue dextran system suitability test solution.* Prepare a solution in mobile phase containing 100 micrograms per milliliter of blue dextran (with a mean molecular weight of approximately 2,000,000).

(ii) *Preparation of working standard and sample solutions*—(*a*) *Working standard solution.* Accurately weigh high molecular weight polymer working standard equivalent to approximately 400 micrograms of high molecular weight polymer into a 100-milliliter volumetric flask and add 80 milliliters of mobile phase. Shake until dissolved and dilute to volume with mobile phase to obtain a solution containing approximately 4 micrograms of high molecular weight polymer per milliliter. Store the solution at ambient temperature and inject into the chromatograph within one hour of preparation.

(*b*) *Sample solution.* Accurately weigh approximately 400 milligrams of the sample into a 100-milliliter volumetric flask and add 80 milliliters of mobile phase. Shake until dissolved, dilute to volume with mobile phase, and immediately inject the solution into the liquid chromatograph.

(iii) *System suitability requirements*—(*a*) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.5 for blue dextran.

(*b*) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 1,500 theoretical plates for blue dextran.

(*c*) *Coefficient of variation.* The coefficient of variation (S_R in percent) of five replicate injections of blue dextran is satisfactory if it is not more than 4 percent.

If the system suitability requirements have been met, then proceed as described in § 436.360(b) of this chapter.

(iv) *Calculations.* Calculate the percent of high molecular weight polymer content as follows:

$$\text{High molecular weight polymer content in percent} = \frac{H_u \times P_s \times 0.1}{H_s \times C_u}$$

where:

H_u=Height of the high molecular weight polymer peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

H_s=Mean height of the high molecular weight polymer peaks in the chromatograms of the high molecular weight polymer working standard;

P_s=High molecular weight polymer content of the high molecular weight polymer working standard solution in micrograms per milliliter; and

C_u=Milligrams of sample per milliliter of sample solution.

[50 FR 48399, Nov 25, 1985; 50 FR 53308, Dec. 31, 1985; 51 FR 2478, Jan. 17, 1986, as amended at 55 FR 11583, Mar. 29, 1990]

§ 442.17 Ceftizoxime sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Ceftizoxime sodium is the sodium salt of [6*R*-[6α, 7β(*Z*)]]-7-[[(2,3-dihydro-2-imino-4-thiazolyl) (methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its ceftizoxime content is not less than 850 micrograms and not more than 995 micrograms of ceftizoxime per milligram on an anhydrous basis.

(ii) Its moisture content is not more than 8.5 percent.

(iii) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 6.0 and not more than 8.0

(iv) It gives a positive identity test.

(v) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for ceftizoxime content, moisture, pH, identity, and crystallinity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams, and 1 package containing approximately 5 grams.

(b) *Tests and methods of assay*—(1) *Ceftizoxime content.* Proceed as directed in § 436.345 of this chapter, preparing the sample solution and calculating the ceftizoxime content as described in paragraphs (e)(1) and (g)(1), respectively, of that section.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(4) *Identity.* The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section, compares qualitatively to that of the ceftizoxime working standard.

(5) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[49 FR 49285, Dec. 19, 1984, as amended at 55 FR 11583, Mar. 29, 1990]

§ 442.17a Sterile ceftizoxime sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ceftizoxime sodium is the sodium salt of [6*R*-[6α,7β(*Z*)]]-7-[[(2,3-dihydro-2-imino-4-thiazolyl) (methoxyimino) acetyl]amino]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) If the ceftizoxime is not packaged for dispensing, its ceftizoxime content is not less than 850 micrograms and not more than 995 micrograms of ceftizoxime per milligram on an anhydrous basis. If the ceftizoxime is packaged for dispensing, its ceftizoxime content is not less than 850 micrograms and not more than 995 micrograms of ceftizoxime per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 115 percent of the number of milligrams of ceftizoxime that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 8.5 percent.

(v) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 6.0 and not more than 8.0.

(vi) It gives a positive identity test.

(vii) It is crystalline.